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ORIGINAL ARTICLE

Exposure to Stress-Dose Steroids and Lethal Septic Shock After In-Hospital Cardiac Arrest: Individual Patient Data Reanalysis of Two Prior Randomized Clinical Trials that Evaluated the Vasopressin–Steroids–Epinephrine Combination Versus Epinephrine Alone

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Abstract

Purpose Low-dose steroids may reduce the mortality of severely ill patients with septic shock. We sought to determine whether exposure to stress-dose steroids during and/or after cardiopulmonary resuscitation is associated with reduced risk of death due to postresuscitation septic shock.

Methods We analyzed pooled, individual patient data from two prior, randomized clinical trials (RCTs). RCTs evaluated vasopressin, steroids, and epinephrine (VSE) during resuscitation and stress-dose steroids after resuscitation in vasopressor-requiring, in-hospital cardiac arrest. In the second RCT, 15 control group patients received open-label, stress-dose steroids. Patients with postresuscitation shock were assigned to a Steroids ($n = 118$) or No Steroids ($n = 73$) group according to an "as-treated" principle. We used cumulative incidence competing risks Cox regression to determine cause-specific hazard ratios (CSHRs) for pre-specified predictors of lethal septic shock (primary outcome). In sensitivity analyses, data were analyzed according to the intention-to-treat (ITT) principle (VSE group, $n = 103$; control group, $n = 88$).

Results Lethal septic shock was less likely in Steroids versus No Steroids group, CSHR, 0.40, 95% confidence interval (CI), 0.20–0.82; $p = 0.012$. ITT analysis yielded similar results: VSE versus Control, CSHR, 0.44, 95% CI, 0.23–0.87; $p = 0.019$. Adjustment for significant, between-group baseline differences in composite cardiac arrest causes such as "hypotension and/or myocardial ischemia" did not appreciably affect the aforementioned CSHRs.

Conclusions In this reanalysis, exposure to stress-dose steroids (primarily in the context of a combined VSE intervention) was associated with lower risk of postresuscitation lethal septic shock.

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Introduction

Patients resuscitated from cardiac arrest requiring vasopressors according to guidelines may experience a "sepsis-like" syndrome characterized by cytokine storm, endotoxemia, coagulopathy, adrenal insufficiency, and treatment-refractory circulatory failure termed postresuscitation shock [1–6]. The postresuscitation systemic inflammatory response syndrome (SIRS) may be partly caused and subsequently amplified by ischemia/reperfusion (I/R)-associated disruption of the intestinal mucosal barrier [3, 7–9]. This can acutely increase the concentrations of bacterial cell wall components and proinflammatory mediators in the systemic circulation [8], thereby contributing to postresuscitation myocardial and multiorgan dysfunction [3, 7–9], hyporesponsiveness of circulating leukocytes, and increased susceptibility to septic complications [3, 10–12]. The severe SIRS-associated need for vasopressors and myocardial dysfunction may contribute to further intestinal hypoperfusion and gut barrier damage, thus perpetuating a potentially lethal, vicious cycle [8].

Steroids may mitigate, suppress, and/or inhibit key events of I/R injury propagation such as peroxidative reactions [13], expression of cell adhesion molecules [14, 15], synthesis of proinflammatory cytokines [e.g., tumor necrosis factor alpha, interleukin (IL)-1 beta (IL-1β), IL-6, and IL-8] [4, 15], release and metabolism of arachidonic acid synthesis and overproduction of nitric oxide, and cell apoptosis [7–9, 15, 16].

In shock states, stress-dose steroids improve vascular responsiveness to vasopressors [17, 18] and preserve monocyte and neutrophil phagocytosis, and dendritic cell function [19–21]. Low-dose steroids may reduce the mortality of severely ill patients with septic shock [22].

Comatose cardiac arrest patients are susceptible to postresuscitation nosocomial infections, particularly pneumonia [1, 2, 11, 12, 23]. The latter is likely due to loss of airways protection, pulmonary contusion and/or aspiration, emergency airway access during cardiopulmonary resuscitation (CPR) and subsequent need for mechanical ventilation [23], and I/R-associated lung injury.

Despite recent positive results on bundled treatments containing steroids [1, 2], the clinical usefulness of steroids per se in cardiac arrest still remains unproven [24]. Nosocomial infections constitute an important cause of postresuscitation mortality [1, 2, 11, 25]. We hypothesized that exposure to stress-dose steroids during and/or after CPR may be associated with reduced risk of death due to postresuscitation infections. We tested this hypothesis by performing an individual patient data-based re-analysis (IPDRA) of prior randomized clinical trials (RCTs) of cardiac arrest that evaluated stress-dose steroid-containing regimens and reported on postresuscitation infections.

Methods

Trial Selection and Data Collection

We searched PubMed and Scopus (articles archived until November 2017) and confirmed that two RCTs evaluated vasopressin, methylprednisolone, and epinephrine during CPR and stress-dose hydrocortisone after CPR, and reported on postresuscitation infections [1, 2] (for details see the online Supplement). The IPDRA protocol and its subsequent amendments were approved by the institutional review boards of the three participating centers [1, 2]. Access to electronic hospital records and electronic/hard-copy archives of departments of Microbiology was authorized to confirm prospectively collected data on infections and culture results and to retrospectively collect data on antibiotic resistance (Supplement). Informed consent requirement was waived.

Data Extraction and Synthesis

We extracted individual data from survivors for ≥4 h with postresuscitation shock from a masterfile containing de-identified data from both studies [1, 2]. We created a Microsoft Excel datafile containing baseline, follow-up, and outcome data (Supplement), and data on postresuscitation infections (i.e., primary site, time of occurrence, causative pathogen, and associated hemodynamic instability and respiratory failure), and the non-neurologic sequential organ failure assessment (SOFA) score on the occurrence of the first postresuscitation infection and episode of septic shock. The pre-specified analysis of physiological and organ dysfunction data was aimed at explaining possible between-group differences in the primary IPDRA outcome. The datafile was created by two unblinded authors (S.D.M. and I.K.) and independently cross-checked in subgroups of 47–48 patients for content accuracy by four blinded coauthors (M.K., C.V., D.M., S.S.). Data analysts were unblinded to steroid use.

Definitions

Applicable definitions of infections and associated severe complications, antibiotic resistance, organ failures, and postresuscitation shock are provided in the Supplement. Infection diagnostic criteria were considered as fulfilled when (1) infection occurrence and focus were confirmed by

recordings of the blinded investigators of the included studies, (2) concurrently recorded patient data (e.g., temperature, white blood cell count, new or aggravation of already present circulatory and/or respiratory failure) suggested a new infection, and (3) the accuracy of investigator-recorded culture results was confirmed by reviewing of hospital records (Supplement).

Poor in-hospital outcome was defined as physical death during patient follow-up or postresuscitation neurologic failure (i.e., Glasgow Coma Score (GCS) ≤ 9 while being circulatory failure-free and ≥ 24 h sedation-free [1, 2, 26]) that was associated with a Cerebral Performance Category (CPC) score of ≥ 3 at the end of the follow-up.

In the included studies [1, 2], cases of blinded observer uncertainty and/or interobserver disagreement regarding postresuscitation complications and death causes were resolved by consensus reached during biweekly investigator meetings; help from blinded infectious diseases specialists was available upon request. In the present IPDRA, cases of uncertainty/disagreement, or discrepancy between current retrospective and prior prospective assessments [23] were also resolved by consensus.

Primary Outcome

Lethal septic shock due to a postresuscitation infection. Infectious complications could include microbiologically confirmed ventilator-associated pneumonia (VAP), ventilator-associated tracheobronchitis (VAT), central venous catheter-related bloodstream infection, bacteremia/fungemia of presumed extrapulmonary origin, urinary tract infection, and "other" infections (e.g., endocarditis, soft tissue infection, viral infection).

Secondary Outcomes

Organ failure-free and ventilator-free days (definitions provided in the Supplement), non-infectious complications of stress-dose steroid treatment (hyperglycemia, peptic ulcer bleeding, and neuromuscular weakness), death due to non-infectious causes, and poor in-hospital outcome.

Statistical Analysis

For reasons detailed in the Statistical Analysis subsection of the Supplement, we treated IPDRA pooled data as if originating from the same, single-center study. This resembles the rarely employed "single trial" meta-analytic approach [27], but the second study's statistical design [2] was partly based on first study's results [1]. Hence, included studies were not mutually independent, and the current IPDRA cannot be termed as "meta-analysis."

We aimed to retrospectively determine possible associations between actual exposure to stress-dose steroids during and/or after CPR and risk of death due to postresuscitation infectious complications. In our second RCT [2], 15 control group patients received open-label stress-dose hydrocortisone [started within approximately 4 h of return of spontaneous circulation (ROSC)] by protocol violation. This might hinder the detection of steroid exposure–outcome association(s) by a "gold-standard" intention-to-treat (ITT) analysis due to assignment of actually steroid-treated patients to a "No Steroids" group. Therefore, in our primary analysis, we used an "as treated" approach.

The Steroids IPDRA group included intervention [i.e., vasopressin–steroids–epinephrine (VSE)] group patients from both studies, who were treated as randomized, plus the aforementioned 15 control patients. Current analysis results might have been biased if the open-label steroids had been given for peri-arrest septic shock in severely ill, post-cardiac arrest patients; in such patients, low-dose steroids are associated with lower mortality [22]. However, such bias risk is highly unlikely, because just 2/15 patients (13.3%) had a recorded diagnosis of pre-arrest septic shock onset and both died within 7 days postresuscitation.

Distribution normality was tested by Kolmogorov–Smirnov test. Dichotomous and categorical variables were compared by two-sided χ^2 or Fisher's exact test. Continuous variables were compared by two-tailed, independent samples t test or Mann–Whitney exact U test. Continuous variables exhibiting normal distributions and measured at multiple time points were analyzed by linear mixed model analysis.

Univariable and Multivariable Cox Regression Analyses

We conducted a cumulative incidence competing risks (CICR) analysis [28, 29] to determine cause-specific hazard ratios (CSHRs) and their 95% confidence intervals (CIs) for lethal septic shock, death due to a non-infectious cause, and poor in-hospital outcome. Regarding lethal septic shock, competing risks included postresuscitation neurologic failure followed by a final in-hospital CPC score of 3 or 4, death due to a non-infectious cause, and survival to hospital discharge with CPC score of 1 or 2. Censoring of observations and exclusion of patients from the risk set [28, 29] was performed either at time points of first detection of poor in-hospital outcome [2], or hospital discharge with a CPC score of 1 or 2. The time frame of the CICR analysis extended up to day 60 after ROSC because in both included studies, 60-day mortality coincided with in-hospital mortality.

Prespecified risk factors for physical death or poor in-hospital outcome [2] were group (Steroids vs. No Steroids); cardiac arrest cause (cardiac vs. non-cardiac); cardiac arrest area (monitored vs. non-monitored), initial cardiac arrest rhythm (shockable vs. non-shockable); cardiac arrest time

(i.e., weekday vs. holiday and nighttime vs. morning-to-late evening), advanced life support (ALS)-related bicarbonate dose; time from resuscitation team call to ALS initiation plus ALS duration; and therapeutic hypothermia (yes vs. no).

Group and risk factors with a univariate analysis p value of ≤ 0.05 for any CSHR were included in the final, primary, multivariable CICR Cox model. Models showing a significant effect of group were to be further adjusted for any significant between-group baseline differences by including the respective baseline patient characteristics as covariates.

In all analyses, the proportional hazards assumption was tested by visually confirming that the "log minus log" curves were parallel. Collinearity assessment comprised determination of variance inflation and condition indexes.

Sensitivity Analyses

We performed additional CICR multivariable analyses according to the ITT principle by substituting the Steroids and No Steroids groups by the original VSE and Control groups of our prior studies [1, 2].

Finally, we added early (i.e., measured within 15–20 min post-ROSC) postresuscitation mean arterial pressure (MAP) [30] to multivariable models showing a significant effect of group. Missing postresuscitation MAP datapoints ($n = 26/191$, 13.6%) were filled by five random imputations. Subsequently, we repeated the CICR analyses five times (with each analysis corresponding to one imputation) and determined pooled CSHRs by inverse variance method [31].

Statistical Software

Statistical significance was accepted at $p < 0.05$. Analyses were performed with SPSS version 22.0 (IBM, Armonk, NY), Amelia version 1.6.4 (Harvard University, Cambridge, MA), and R version 3.2.4 (R Foundation, Vienna, Austria).

Results

Baseline and Peri-Arrest Data

Table 1 displays baseline characteristics. Significant between-group differences included age, acute renal disease as hospital admission cause, and hypotension and metabolic disturbance as cause of cardiac arrest ($p \leq 0.047$). Significant differences in cardiac arrest causes had an absolute magnitude of approximately 10–16%; between-group differences became more marked (approximate magnitude, 18–22%; $p \leq 0.011$) when these data were analyzed according to "composite cardiac arrest causes," such as "hypotension and/or myocardial ischemia" and "respiratory depression/failure and/or metabolic disturbance" (Table 1). Notably, slightly smaller (i.e., by approximately 1–3%) differences in cardiac arrest causes were also observed when the IPDRA population was subdivided in VSE and Control groups (Supplement, Table S1). Further analyses of data from the total VSE 1 and 2 population ($n = 368$) revealed substantially (i.e., by approximately 5–10%) smaller but still significant ($p = 0.044$ to 0.046) between-group imbalances in the aforementioned "non-composite" cardiac arrest causes (Table S1); similar baseline imbalances (i.e., of $\leq 10\%$) among study groups of comparable size have been previously reported by others as well [32]. Differences in the magnitude of baseline imbalances between the current IPDRA groups and the pooled study groups of the VSE 1 and 2 studies reflect the exclusion from the current IPDRA of VSE 1 and 2 patients who (1) did not achieve ROSC, (2) survived for < 4 h after ROSC, and (3) did not fulfill the pre-specified criteria for postresuscitation shock (Table S1; see also pertinent definition in the eMethods section of the Supplement).

Proportions of patients with a recorded diagnosis of pre-arrest infection with or without septic shock were similar ($p = 0.49$ to 0.84; Table 1). Among pre-arrest septic shock patients, just one Steroids group participant survived to hospital discharge. ALS and peri-arrest physiological data and early postresuscitation support are detailed in the Supplement. Total CPR epinephrine dose and time to ALS initiation plus ALS duration did not differ significantly between Steroids and No Steroids group ($p = 0.09$ to 0.16). Peri-arrest arterial pressure was higher in Steroids versus No Steroids group ($p \leq 0.01$). Data on therapeutic hypothermia are detailed in the Supplement.

Early Follow-Up Physiological Data

Details are presented in the Supplement. During days 1–10, MAP and central venous oxygen saturation were higher in Steroids versus No Steroids group (effect of group, $p < 0.001$).

Infectious Complications

Table 2 displays postresuscitation infection and antibiotic resistance data (see also the Supplement). During included studies' conduct and current IPDRA, consensus had to be respectively reached for 19/133 (14.3%) and 12/138 (8.7%; 138 = 133 plus 5 cases of VAT not originally reported [1, 2]) episodes of confirmed and/or suspected infection, and for 3/155 (2.0%) causes of death. As consensus was ultimately reached in all cases, there was no further assessment of any inter-rater agreement.

Proportions of patients with ≥ 1 postresuscitation infection, median times to first infection, and non-renal SOFA subcomponent scores on first infection onset did not differ significantly between groups. On first infection occurrence, Steroids versus No Steroids group had lower renal SOFA subcomponent scores and non-neurologic SOFA scores ($p \leq 0.03$;

Table 1 Patient characteristics before cardiac arrest and causes of cardiac arrest

Characteristic	Steroids ($n = 118$)	No Steroids ($n = 73$)	p value
Age, median (IQR)	68 (49–77)	73 (59–78)	0.047
Male sex, *n* (%)	81 (68.6)	49 (67.1)	0.48
Body mass index, median (IQR), kg/m^2	25 (23–28)	24 (23–27)	0.44
Pre-arrest hospital stay, median (IQR), days[a]	4 (1–9)	3 (1–7)[**72**]	0.36
Comorbidity			
Cardiovascular			
Hypertension, *n* (%)	56 (47.5)	41 (56.2)	0.30
Coronary artery disease, *n* (%)	36 (30.5)	26 (35.6)	0.53
Diabetes, *n* (%)	25 (21.2)	15 (20.5)	> 0.99
Peripheral vascular disease, *n* (%)	23 (19.5)	17 (23.3)	0.59
Cardiac arrhythmia, *n* (%)	17 (14.4)	14 (19.2)	0.42
Valvular heart disease, *n* (%)	14 (11.9)	9 (12.3)	> 0.99
Cardiac conduction disturbances, *n* (%)	10 (8.5)	5 (6.8)	0.79
Non-cardiovascular, *n* (%)[b]	71 (60.2)	47 (64.4)	0.65
Hospital admission cause[c]			
Medical, *n* (%)	83 (70.3)	50 (68.5)	0.87
Acute cardiovascular disease, *n* (%)	36 (30.5)	22 (30.1)	> 0.99
Acute respiratory disease, *n* (%)	20 (16.9)	19 (26.0)	0.14
Acute digestive disease, *n* (%)	21 (17.8)	17 (23.3)	0.46
Acute neurologic disease, *n* (%)	18 (15.3)	5 (6.8)	0.11
Trauma, *n* (%)	11 (9.3)	5 (6.8)	0.60
Malignancy, *n* (%)	12 (10.2)	9 (12.3)	0.81
Acute renal disease, *n* (%)	3 (2.5)	7 (9.6)	0.045
Other, *n* (%)	10 (8.5)	3 (4.1)	0.38
Pre-arrest infection without septic shock[d], *n* (%)	17 (14.4)	12 (16.4)	0.82
Pre-arrest septic shock[e], *n* (%)	12 (10.2)	10 (13.7)	0.49
Cause of cardiac arrest[f]			
Hypotension, *n* (%)	49 (41.5)	19 (26.0)	0.04
Respiratory depression or failure, *n* (%)	41 (34.7)	33 (45.2)	0.17
Myocardial ischemia/infarction, *n* (%)	28 (23.7)	10 (13.7)	0.10
Metabolic, *n* (%)	9 (7.6)	13 (17.8)	0.04
Lethal arrhythmia, *n* (%)	8 (6.8)	5 (6.8)	> 0.99
Other[g], *n* (%)	2 (1.7)	3 (4.1)	0.37
Hypotension and/or myocardial ischemia/infarction, *n* (%)[f]	73 (61.9)	29 (39.7)	0.004
Respiratory depression or failure and/or metabolic cause, *n* (%)[f]	50 (42.4)	45 (61.6)	0.011

IQR interquartile range, *SD* standard deviation

[a] Exponent in bold indicates the number of the "No Steroids group" patients participating in the analysis (i.e., 72) as this number was lower than the maximal possible of 73

[s] Includes chronic respiratory, neurologic, digestive, renal, endocrine, autoimmune, and musculoskeletal disease, malignancy, and immunosuppression. Six of 91 patients (6.6%) of the Steroids group and 6 of 58 patients (10.3%) of the No Steroids group ($p = 0.54$ vs. Steroids group) had prior treatment with inhaled steroids; there were no available, pertinent data on the 42 participants from our first randomized study (reported in reference 1)

[c] Some patients had more than one cause of hospital admission; "other" causes included two cases of acute pyelonephritis causing septic shock, and one case of left lower extremity gangrene, scheduled resection of a benign tumor, portal vein thrombosis, visceral hemangiomatosis, diabetic ketoacidosis, cervical abscess, rheumatoid arthritis exacerbation, scheduled bone marrow transplantation, pheochromocytoma, immunosuppression-associated sepsis, and amyloidosis

[d,e] Such complications had to be recorded as clinically suspected/microbiologically confirmed by positive cultures of specimens taken before the occurrence of the cardiac arrest

[f] In some patients, there were more than one major disturbances and/or "composite cardiac arrest causes" precipitating the cardiac arrest. Steroids versus No Steroids group proportions of patients with both "composite cardiac arrest causes," 12/118 (10.2%) vs. 6/73 (6.8%), $p = 0.60$

[g] Includes two cases of drug toxicity and one case of permanent pacemaker malfunction, vagotonic arrest, and intracerebral hemorrhage

Table 2 Postresuscitation infectious complications

Type of infection and pathogens		Steroids	No Steroids	
		($n = 118$)	($n = 73$)	p value
VAP 1st episode[a]—pathogen, n (%)	*A. baumannii*[b]	18 (15.3)	5 (6.9)	
	K. pneumoniae[c,d]	12 (10.2)	8 (11.0)	
	P. aeruginosa[e]	10 (8.5)	2 (2.7)	
	MRSA	1 (0.8)	2 (2.7)	
	Pr. mirabilis	1 (0.8)	1 (1.4)	
	E. aerogenes	0 (0.0)	1 (1.4)	
At least 1 episode of VAP, n (%)		42 (35.6)	19 (26.0)	0.20
Septic shock during VAP 2nd episode, n (%)		34 (28.8)	15 (20.5)	0.24
VAP 2nd Episode[a]—pathogen, n (%)	*P. aeruginosa*	5 (4.2)	3 (4.1)	
	K. pneumoniae	3 (2.5)	1 (1.4)	
	A. baumannii	2 (1.7)	0 (0.0)	
	Prov. stuartii	1 (0.8)	0 (0.0)	
At least 2 episodes of VAP, n (%)		11 (9.3)	4 (5.5)	0.42
Septic shock during VAP 2nd episode, n (%)		4 (5.5)	7 (5.9)	> 0.99
VAP 3rd episode[a]—pathogen, n (%)	*K. pneumoniae*	2 (1.7)	1 (1.4)	
3 Episodes of VAP, n (%)		2 (1.7)	1 (1.4)	> 0.99
Septic shock during VAP 3rd episode, n (%)		1 (0.8)	1 (1.4)	> 0.99
Type of infection and pathogens		Steroids	No steroids	
		($n = 118$)	($n = 73$)	p value
VAT[a]—pathogen, n (%)	*A. baumannii*[f]	2 (1.7)	0 (0.0)	
	K. pneumoniae[g]	0 (0.0)	1 (1.4)	
	P. aeruginosa	0 (0.0)	1 (1.4)	
	S. maltophilia[h]	1 (0.8)	0 (0.0)	
VAT, n (%)		3 (2.5)	2 (2.7)	> 0.99
Septic shock during VAT, n (%)		2 (1.7)	2 (2.7)	0.64
Lethal septic shock—pathogen, n (%)	*K. pneumoniae*[i]	11 (9.3)	10 (13.7)	
	A. baumannii[k]	3 (2.5)	1 (1.4)	
	P. aeruginosa[l]	2 (1.7)	1 (1.4)	
	Pr. mirabilis[m]	0 (0.0)	1 (1.4)	
	Prov. stuartii[n]	0 (0.0)	1 (1.4)	
	E. aerogenes[o]	0 (0.0)	1 (1.4)	
	R. radiobacter[p]	1 (0.8)	0 (0.0)	
	Str. pyogenes[q]	1 (0.8)	0 (0.0)	
	C. glabrata[r]	1 (0.8)	0 (0.0)	
	C. parapsilosis[s]	0 (0.0)	1 (1.4)	
	T. asachii[t]	1 (0.8)	0 (0.0)	
Lethal septic shock, n (%)		***20 (16.9)***	***16 (21.9)***	***0.45***
Lethal septic shock in survivors for ≥ 48 h, n/total N (%)		***20/83 (24.1)***	***16/37 (43.2)***	***0.051***
Catheter-related bacteremia—pathogen, n (%)	*Prov. stuartii*	2 (1.7)	1 (1.4)	
	K. pneumoniae	0 (0.0)	1 (1.4)	
	P. aeruginosa	1 (0.9)	0 (0.0)	
	C. parapsilosis	1 (0.9)	0 (0.0)	
Catheter-related bacteremia, n (%)		4 (3.4)	2 (2.7)	> 0.99
Septic shock during catheter-related bacteremia, n (%)		4 (3.4)	2 (2.7)	> 0.99
Urinary tract infection—pathogen, n (%)	*P. aeruginosa*	2 (1.7)	1 (1.4)	
	A. baumannii	0 (0.0)	1 (1.4)	
	E. aerogenes	0 (0.0)	1 (1.4)	
	Pr. mirabilis	1 (0.8)	0 (0.0)	
	C. tropicalis	1 (0.8)	0 (0.0)	
Urinary tract infection, n (%)		4 (3.4)	3 (4.1)	> 0.99
Septic shock during urinary tract infection, n (%)		1 (0.8)	2 (2.7)	0.60
Other complication—endocarditis—pathogen, n (%)	*K. pneumoniae*	1 (0.8)	1 (1.4)	
	A. baumannii	1 (0.8)	0 (0.0)	
Transfusion-related	*CMV*[u]	1 (0.8)	0 (0.0)	
Soft tissue infection	*Str. pyogenes*[v]	1 (0.8)	0 (0.0)	
Other infectious complication, n (%)		4 (3.4)	1 (1.4)	0.65
Septic shock during other infectious complication, n (%)		4 (3.4)	1 (1.4)	0.65
Antibiotic resistance[x]		Steroids	No Steroids	
		($n_I = 82$)[y]	($n_I = 46$)[y]	p value
Infection due to XDR pathogen, n (%)		50 (61.0)	31 (67.4)	0.57
Infection due to MDR pathogen, n (%)		23 (28.0)	13 (28.3)	> 0.99
Infection due to non-MDR pathogen, n (%)		6 (7.3)	1 (2.2)	0.42

Table 2 (continued)

Type of infection and pathogens	Steroids	No Steroids	
	($n = 118$)	($n = 73$)	p value
Infection due to fungus, n (%)	3 (3.7)	1 (2.2)	> 0.99

Summary data pertaining to the primary outcome are highlighted in italic bold script

SOFA, sequential organ failure assessment; *VAP*, ventilator-associated pneumonia; *VAT*, ventilator-associated tracheobronchitis; *A.*, *Acinetobacter*; *K.*, *Klebsiella*; *P.*, *Pseudomonas*; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *Pr.*, *Proteus*; *E.*, *Enterobacter*; *Prov.*, *Providenzia*; *S.*, *Stenotrophomonas*; *R.*, *Rhizobium*; *Str.*, *Streptococcus*; *C.*, *Candida*; *T.*, *Trichosporon*; *CMV*, *Cytomegalovirus*; *XDR*, extensively drug-resistant; *MDR*, multidrug-resistant

[a] VAP, first episode was caused by multidrug-resistant (MDR)/extensively drug-resistant (XDR) bacteria in 16/25 patients of the Steroids group and 3/16 patients of the No Steroids group; in addition, there was 1 case of VAP by a non-MDR bacterium in each group; VAP second episode was caused by MDR/XDR bacteria in 3/8 patients of the Steroids group and 2/2 patients of the No Steroids group; VAP third episode was caused by XDR bacteria in 2 patients of the Steroids group and 1 patient of the No Steroids group; VAT was caused by MDR/XDR bacteria in 0/3 patients of the Steroids group and 1/1 patient of the No Steroids group

[b] Temporally associated with (i.e., diagnosis established within 72 h prior to) acute respiratory distress syndrome (ARDS) in 2 patients of the Steroids group and 1 patient of the No Steroids group

[c] Temporally associated with ARDS in 8 patients of the Steroids group and 4 patients of the No Steroids group

[d] VAP occurred in 1 patient of the No Steroids group on day 1 postarrest; the patient was transferred intubated and mechanically ventilated from another hospital before the cardiac arrest and the total time on mechanical ventilation before VAP diagnosis was 4 days

[e] Temporally associated with ARDS in 4 patients of the Steroids group and 1 patient of the No Steroids group

[f] Temporally associated with ARDS in 2 patients of the Steroids group

[g] Temporally associated with ARDS in 1 patient of the No Steroids group

[h] Temporally associated with ARDS in 1 patient of the Steroids group

[i] Cultures of blood isolates revealed XDR *K. pneumoniae* in 20 cases of both groups and MDR *K. pneumoniae* in 1 case of the No Steroids group; septic shock causing death occurred within 7 days of VAP onset by an XDR and/or an MDR pathogen in 10 patients of the Steroids group (with 6 patients also developing ARDS) and 4 patients of the No Steroids group (with 2 patients also developing ARDS); in 1 patient of the No Steroids group, lethal septic shock occurred within 1 day of onset of VAT by XDR *K. pneumoniae*; in 1 patient of the Steroids group, lethal septic shock occurred in the presence of clinical suspicion of acalculus cholecystitis; in 4 patients of the No Steroids group, lethal septic shock occurred as a complication of intra-abdominal sepsis (2 cases of postoperative abscess formation, 1 case of Crohn's disease-related abscess formation, and 1 case of suspected acalculus cholecystitis); in 1 patient of the No Steroids group, lethal septic shock occurred as a complication of catheter-related infection by XDR *K. pneumoniae*

[k] Cultures of blood isolates revealed XDR *A. baumannii* in 3 cases (No Steroids group, $n = 1$) and MDR *A. baumannii* in 1 case; septic shock causing death occurred within 5 days of VAP onset by an XDR and/or an MDR pathogen in 3 patients of the Steroids group (with 1 patient also developing ARDS); in 1 patient of the No Steroids group, lethal septic shock due to presumed cholangitis occurred within 48 h of endoscopic retrograde cholangiopancreatography for pre-arrest-confirmed choledocholithiasis

[l] Cultures of blood isolates revealed XDR *P. aeruginosa* in 2 cases (No Steroids group, $n = 1$) and MDR *P. aeruginosa* in 1 case; septic shock causing death occurred within 1 day of VAP onset by an XDR and/or an MDR pathogen in 2 patients of the Steroids group (with both also developing ARDS); in 1 patient of the No Steroids group

[m] Cultures of blood isolates revealed MDR *Pr. mirabilis* in 1 patient of the No Steroids group; septic shock causing death occurred within 4 days of VAP onset by XDR *E. aerogenes*

[n] Cultures of blood isolates revealed MDR *Prov. stuartii* in 1 patient of the No Steroids group; septic shock causing death occurred within 5 days of onset of urinary tract infection by MDR *E. aerogenes*

[o] Cultures of blood isolates revealed MDR *E. aerogenes* in 1 patient of the No Steroids group; septic shock causing death occurred within 3 days of onset of VAP by MDR MRSA

[p] Cultures of blood isolates revealed non-MDR *R. radiobacter* in 1 patient of the Steroids group; septic shock causing death and ARDS occurred within 1 day of onset of VAP by XDR *A. baumannii*

[q] Cultures of blood isolates revealed non-MDR *Str. pyogenes*; septic shock causing death occurred within 4 days of onset of soft tissue infection by the aforementioned pathogen

[r] Cultures of blood isolates revealed fluconazole-resistant *C. glabrata*; septic shock causing death occurred within 2 days of onset of peritonitis that followed ERCP for choledocholithiasis—cholelithiasis was already confirmed during pre-arrest hospital stay

[s] Cultures of blood isolates revealed fluconazole-resistant *C. parapsilosis*; septic shock causing death and ARDS occurred within 2 days of onset of peritonitis secondary to suspected postenterectomy anastomosis leakage

[t] Cultures of blood isolates revealed Amphotericin B and voriconazole-susceptible *T. asachii* causing poststernotomy sternal osteomyelitis and mediastinitis and lethal septic shock

[u] Associated with severe bilateral pneumonia and ARDS

[v] Associated with lethal septic shock by the same pathogen

[x] Definitions provided in the eMethods section of the Supplement

[y] n_I reflects number of episodes of postresuscitation infections that occurred in 48 and 25 patients of the Steroids and No Steroids group, respectively

Supplement, Table S5). One or more episodes of septic shock occurred in 42/118 (35.6%) vs. 25/73 (35.2%) patients of Steroids versus No Steroids group ($p = 0.88$). On septic shock occurrence, Steroids versus No Steroids group had lower renal SOFA subcomponent scores ($p = 0.001$); median times to septic shock, other SOFA subcomponent scores, and non-neurologic SOFA scores did not differ significantly (Table S5).

The frequency of postresuscitation lethal septic shock did not differ significantly between groups (Steroids vs. No Steroids, 16.9% vs. 21.9%; $p = 0.45$). However, after "risk-set exclusion" of survivors for < 48 h, i.e., of patients who died (competing event) before follow-up day 3 (time of earliest death due to postarrest septic shock), lethal septic shock frequency was 19.1% lower in steroid-treated versus placebo-treated patients (24.1% vs. 43.2%; $p = 0.051$) (Table 2).

Organ Dysfunction During Follow-Up

The Steroids versus No Steroids group had significantly more circulatory, coagulation, hepatic, neurologic, renal, and respiratory failure-free days and ventilator free days ($p \leq 0.04$; Supplement).

Univariable and Multivariable Analyses

Primary analysis results on lethal septic shock are displayed in Table 3 and Fig. 1a. Lethal septic shock was predicted by group (Steroids vs. No Steroids, CSHR, 0.40, 95% CI, 0.20–0.82; $p = 0.012$). Death of non-infectious causes (Table 3 and Fig. 1b) and poor in-hospital outcome (Table 4 and Fig. 1e) were predicted by group and ALS-related bicarbonate dose.

Sensitivity (ITT) analysis results on lethal septic shock are presented in Table 3 and Fig. 1c. Lethal septic shock was predicted by group (VSE vs. Control, CSHR, 0.44, 95% CI, 0.23–0.87; $p = 0.019$). Death of non-infectious causes (Table 3 and Fig. 1d) was predicted by time to ALS initiation and ALS duration, and ALS-related bicarbonate dose. Poor in-hospital outcome (Table 4 and Fig. 1f) was predicted by group and ALS-related bicarbonate dose.

The addition of early post-ROSC MAP as covariate did not substantially modify the precision of group effect estimates for lethal septic shock ($p = 0.012$ to 0.034 and $p = 0.016$ to 0.058 in the "as treated" and ITT analyses, respectively; Supplement, Table S7). The pooled CSHRs for five MAP-including analyses were favorable for Steroids versus No Steroids (0.41, 95% CI, 0.29–0.58; $p < 0.001$) and for VSE versus Control (0.44, 95% CI, 0.31–0.62; $p < 0.001$).

A post hoc adjustment of the primary and ITT analyses according to the "composite cardiac arrest cause" of "hypotension and/or myocardial ischemia" (Supplement, Tables S8 and S9) did not appreciably modify the CSHRs of the aforementioned predictors of lethal septic shock, death of non-infectious causes, and poor in-hospital outcome (see also Tables 3 and 4, and Fig. 1). Furthermore, "hypotension and/or myocardial ischemia" was not an independent predictor of patient outcomes ($p \geq 0.24$). Lastly, a Cox regression analysis using the pooled data from all the 368 VSE 1 and 2 patients did not reveal any significant effect of the "composite cardiac arrest cause" of "respiratory depression/failure and/or metabolic disturbance" on poor in-hospital outcomes ($p = 0.61$; Supplement, Table S10).

Complications, Medication During Follow-Up, and Causes of Death

Additional details are reported in the Supplement. Steroids versus No Steroids group had more episodes of hyperglycemia, and more patient-days of insulin and antiarrhythmics use. Coexisting, severe neurological injury could not be excluded in 117/155 of observed deaths (75.5%); 87/155 (56.1%) were caused by early postresuscitation multiple organ failure [2, 26]. During follow-up, these patients were never neurologically evaluated while being free of circulatory failure or not receiving sedation for ≥ 24 h [26], and could never be rated as neurologic failure-free. Seven/155 patients (4.5%; No Steroids group, $n = 2$) had intracranial pressure-monitoring or computed tomographic evidence of cardiac arrest-induced aggravation of pre-existing intracranial pathology. Another 16/155 patients (10.3%; No Steroids group, $n = 9$) had a first neurological evaluation GCS score of ≤ 9 while being circulatory failure free and ≥ 24 h sedation free. The neurologic failure persisted during follow-up, indicating cardiac arrest-associated neurological injury. This was considered as the major determinant of their subsequent intensive care dependence and physical death [26]. In the CICR analysis, observations from this subgroup were censored at the time point of the first, pos-ROSC neurological evaluation.

Discussion

In the current IPDRA, exposure to stress-dose steroids during and/or after CPR was associated with a 60% reduction in the hazard of death due to postresuscitation septic shock. This was partly explanatory of the favorable CSHR for poor in-hospital outcome. ITT sensitivity analysis results were similar. The potential, sepsis-related clinical benefit is consistent with the lower renal SOFA subcomponent scores on septic shock occurrence (median time, 6–7 days postarrest; Supplement, Table S5) [33] and lower non-neurologic SOFA scores on first infection occurrence (median time, 6–7 days postarrest; Table S5). This steroid-associated attenuation of organ dysfunction is in line with the higher

Table 3 Lethal septic shock: results of univariable and multivariable competing risks analyses

Univariable analysis	Lethal septic shock			Death due to non-infectious causes(s)		
Risk factor	CSHR	95% CI	*p* value	CSHR	95% CI	*p* value
Group (Steroids vs. No Steroids)	0.41	0.21–0.81	0.01	0.61	0.42–0.87	0.007
Cause (cardiac vs. non-cardiac)	0.55	0.23–1.33	0.19	1.02	0.69–1.52	0.92
Area (monitored vs. non-monitored)	1.58	0.82–3.03	0.17	1.00	0.67–1.44	0.97
Presenting rhythm (shockable vs. non-shockable)	0.92	0.36–2.38	0.87	1.13	0.72–1.79	0.59
Holiday vs. working day	0.86	0.36–2.07	0.73	0.95	0.59–1.53	0.84
Night (23:00–07:00) vs. morning-to-late evening (07:00–23:00)	1.10	0.50–2.43	0.81	1.07	0.69–1.64	0.77
Time to ALS initiation plus ALS duration (min)	0.96	0.92–1.00	0.07	1.02	1.01–1.03	0.001
$NaHCO_3$ dose in units of 45 mmol	0.82	0.61–1.11	0.19	1.25	1.13–1.38	< 0.001
Therapeutic hypothermia (yes vs. no)	1.26	0.65–2.45	0.49	0.78	0.52–1.16	0.22
Primary multivariable analysis	Lethal septic shock			Death due to non-infectious causes(s)		
Risk factor	CSHR	95% CI	*p* value	CSHR	95% CI	*p* value
Group (Steroids vs. No Steroids)	0.40	0.20–0.82	0.012	0.59	0.40–0.87	0.007
Time to ALS initiation plus ALS duration (min)	0.97	0.93–1.01	0.12	1.01	1.00–1.02	0.06
$NaHCO_3$ dose in units of 45 mmol	0.92	0.65–1.30	0.63	1.28	1.14–1.42	< 0.001
Age (years)	1.01	0.99–1.03	0.34	1.01	1.00–1.02	0.09
Hospital admission due to acute renal disease (yes vs. no)	1.38	0.28–7.11	0.70	0.51	0.21–1.25	0.14
Cardiac arrest due to hypotension (yes vs. no)	1.49	0.72–3.08	0.28	1.29	0.88–1.90	0.19
Cardiac arrest due to metabolic disturbance (yes vs. no)	0.80	0.19–3.37	0.77	1.35	0.75–2.45	0.32
Sensitivity multivariable analysis[a]	Lethal septic shock			Death due to non-infectious causes(s)		
Risk factor	CSHR	95% CI	*p* value	CSHR	95% CI	*p* value
Group (VSE vs. Control)	0.44	0.23–0.87	0.019	0.73	0.50–1.05	0.088
Time to ALS initiation plus ALS duration (min)	0.97	0.93–1.01	0.13	1.01	1.00–1.02	0.03
$NaHCO_3$ dose in units of 45 mmol	0.86	0.61–1.20	0.36	1.22	1.10–1.35	< 0.001
Cardiac arrest due to metabolic disturbance[a] (yes vs. no)	0.92	0.31–2.72	0.88	1.07	0.63–1.84	0.80

CSHR cause-specific hazard ratio, *CI* confidence interval, *ALS* advanced life support, *VSE* vasopressin–steroids–epinephrine. Collinearity diagnostics data: (1) primary analysis: variance inflation, 1.04–1.18; condition index, 14.99; (2) sensitivity analysis: variance inflation, 1.04–1.11; condition index, 4.24

[a] Analysis adjusted for the sole baseline difference not pertaining to a "composite cardiac arrest cause" between the combined VSE and control subgroups of survivors for ≥ 4 h with postresuscitation shock of the included studies [1, 2] (intention-to-treat analysis); this difference pertained to "cardiac arrest due to metabolic disturbance": VSE vs. Control, 7/103 (6.8%) vs. 15/88 (17.0%); $p = 0.04$ (see also Table S1 of the Supplement)

postresuscitation MAP (Table S3 and Fig. S4) [1, 2, 33, 34], the lower postresuscitation IL-6 levels reported by the VSE 1 study [1], and, ultimately, our mechanistic hypothesis of steroid inhibition of I/R injury propagation and attenuation of the associated SIRS and vasodilatory shock.

The potential lethal septic shock benefit might be partly attributable to the CPR subcomponent of the VSE regimen [1, 2]. However, a major CPR VSE effect, i.e., significantly lower number of vasopressor doses and CPR cycles resulting in shorter ALS duration [2], was not apparent in the current IPDRA subpopulation of our prior studies (Table S2). Furthermore, the adjustment of the "as treated" and ITT lethal septic shock models for early post-ROSC MAP still resulted in favorable, pooled CSHRs for steroid-containing regimens ("Results" section and Table S7); the observed, higher post-ROSC MAP in steroid-treated patients (Table S3 and Fig. S4) could be explained by a possible synergy between vasopressin and steroids [2].

A recent RCT of 38 out-of-hospital and 12 in-hospital cardiac arrest patients with postresuscitation shock [35] reported no stress-dose hydrocortisone versus placebo difference in times to or rates of shock reversal and clinical outcomes; in steroid-treated patients, IL-6 levels were lower at 24 h postenrollment. Data on post-ROSC MAP or infectious complications were not reported. The median post-ROSC time to steroid initiation was 9.9 h [35]. This delay likely exceeded the therapeutic window for a stress-dose steroid prevention of potentially detrimental episodes of early post-ROSC hypotension and steroid inhibition of I/R injury propagation [30, 34, 36]. These plausible explanations are supported by a recent, large ($n = 8628$) propensity score-matched analysis, which showed an association between favorable clinical outcomes and steroids during CPR [37].

Current IPDRA data analyses on shock reversal and day 1 hemodynamic support data also showed no between-group difference (Table S4). However, the Steroids versus No

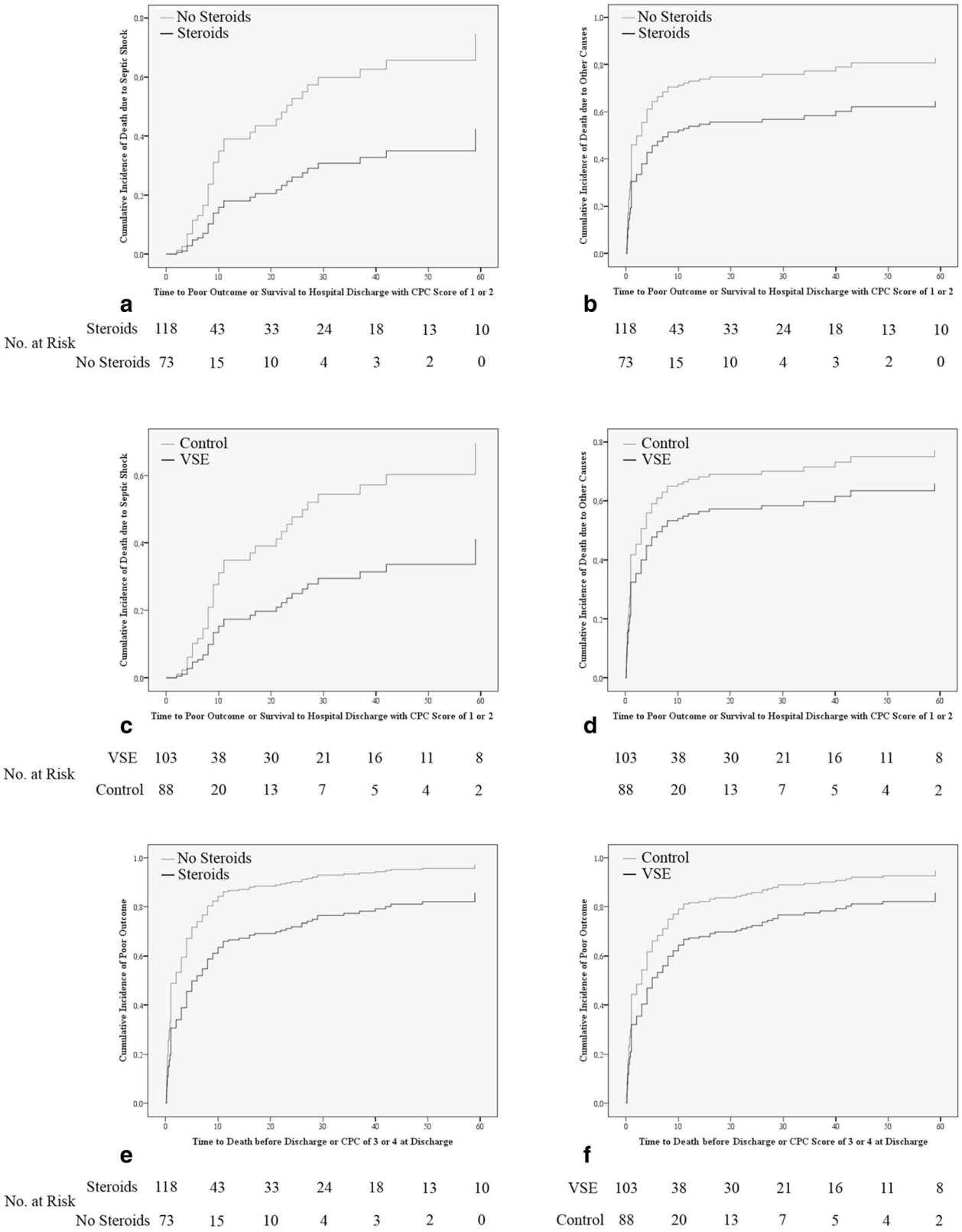

Fig. 1 Results of the competing risks analyses. **a**, **b** "As treated" primary analysis: cumulative incidence functions for lethal septic shock (**a**) and death due to non-infectious causes (**b**). **c**, **d** Intention-to-treat, sensitivity analysis: cumulative incidence functions for lethal septic shock (**c**) and death due to non-infectious causes (**d**). **e** "As treated" primary analysis: cumulative incidence function for poor in-hospital outcome. **f** Intention-to-treat, sensitivity analysis: cumulative incidence function for poor in-hospital outcome. CPC, cerebral performance category; VSE, vasopressin–steroids–epinephrine

Table 4 Results of multivariable analyses on all-cause in-hospital mortality or survival to discharge with a CPC score of 3 or 4

Primary multivariable analysis	All-cause mortality or survival to hospital discharge with CPC score of 3 or 4		
Risk factor	CSHR	95% CI	*p* value
Group (Steroids vs. No Steroids)	0.55	0.39–0.76	< 0.001
Time to ALS initiation plus ALS duration (min)	1.00	0.99–1.01	0.44
$NaHCO_3$ dose in units of 45 mmol	1.22	1.10–1.34	< 0.001
Age (years)	1.01	1.00–1.02	0.15
Hospital admission due to acute renal disease (yes vs. no)	0.55	0.26–1.18	0.13
Cardiac arrest due to hypotension (yes vs. no)	1.26	0.91–1.76	0.17
Cardiac arrest due to metabolic disturbance (yes vs. no)	1.22	0.72–2.07	0.46
Sensitivity multivariable analysis[a]	All-cause mortality or survival to hospital discharge with CPC score of 3 or 4		
Risk factor	CSHR	95% CI	*p* value
Group (VSE vs. Control)	0.66	0.48–0.90	0.01
Time to ALS initiation plus ALS duration (min)	1.01	1.00–1.02	0.23
$NaHCO_3$ dose in units of 45 mmol	1.16	1.05–1.27	0.002
Cardiac arrest due to metabolic disturbance [a] (yes vs. no)	1.01	0.63–1.62	0.96

CPC cerebral performance category, *CSHR* cause-specific hazard ratio, *CI* confidence interval, *ALS* advanced life support, *VSE* vasopressin–steroids–epinephrine. Collinearity diagnostics data: (1) primary analysis: variance inflation, 1.04–1.18; condition index, 14.99; sensitivity analysis: variance inflation, 1.04–1.11; condition index, 4.24

[a] Analysis adjusted for the sole baseline difference not pertaining to a "composite cardiac arrest cause" between the combined VSE and control subgroups of survivors for ≥ 4 h with postresuscitation shock of the included studies [1, 2] (intention-to-treat analysis); this difference pertained to "cardiac arrest due to metabolic disturbance": VSE vs. Control, 7/103 (6.8%) vs. 15/88 (17.0%); $p = 0.04$ (see also Table S1 of the Supplement)

Steroids group had more patients with early post-ROSC systolic arterial pressure > 90 mmHg, and ≥ 1 day-1 MAP value > 80 mmHg, and such "non-hypotensive" patients had better clinical outcomes (Table S4) [30, 34, 36].

Limitations

The external validity of the current IPDRA remains limited to that of the two included studies [1, 2], the results of which may still warrant replication by future, large multinational trials. These studies were conducted within the National Healthcare System of Greece either at Evaggelismos hospital only [1] or at Evaggelismos hospital and another two centers [2] by the same main investigators, and enrolled similar patients. Furthermore, both studies evaluated the VSE combination—not stress-dose steroids alone—in cardiac arrest, and therefore it has been impossible to precisely determine the relative contribution of the steroids to the observed, positive results [1, 2].

Additional IPDRA limitations include a partly retrospective data collection (i.e., antibiogram data), and an "as-treated" rather than an "as-randomized" primary data analysis. The latter eliminates group cross-contamination due to protocol violation(s), but may result in baseline, between-group imbalances in potentially "effect-modifying" patient characteristics (Table 1 and Table S1) [38]. In fact, and especially as regards the substantial imbalances in cardiac arrest causes (Table 1 and Table S1), one could reasonably argue that the IPDRA (and ITT) groups were fundamentally different. Nevertheless, according to the results of our primary, ITT, and post hoc analyses (see also Tables S8–S10), the aforementioned imbalances did not have any significant effect on patient outcomes or appreciably modify the CSHRs for the exposure to steroids during and/or after CPR. The establishment of causality between stress-dose steroids and prevention of post-ROSC lethal septic shock warrants future, prospective RCT testing.

Finally, as 117/155 deaths (75.5%) occurred after resuscitation from non-shockable rhythms, our data on causes of death do not contradict prior postresuscitation mode-of-death reports ("Results" section and Supplement text, and Table S1) [26]. In Greece, besides clinically established brain death diagnosis, there is no specific legal support or criteria for life support withdrawal due to neurological injury [39].

Conclusions

In this IPDRA, stress-dose steroids (used primarily in the context of a combined VSE intervention) were associated with lower risk of postresuscitation lethal septic shock. Any potential, pertinent causality requires future RCT confirmation.

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Study concept: N.M., S.D.M. *Study design:* S.D.M., N.M., T.X., S.Z. *PubMed and Scopus search and study selection:* I.K., S.D.M. *Extraction of data:* I.K., S.D.M. *Cross-checking for pooled data accuracy*: M.K., C.V., D.M., G.K. *Retrospective collection of microbiological data*: I.K., S.D.M., D.M., E.Z., S.S., S.A. *Drafting of the manuscript:* S.D.M. *Critical revision of the manuscript for important intellectual content:* all authors. *Statistical expertise:* S.D.M., C.V., M.K. *Statistical supervision:* S.D.M. *Full access to all of the data in the IPDRA and responsibility for the integrity of the data and the accuracy of the data and analysis:* S.D.M.

Study Organization.

Study chairpersons: S.D.M. and S.Z.

Compliance with Ethical Standard

Conflict of Interest Statement The authors declare that they have no conflict of interest.

Ethical Approval and Informed Consent The individual patient data-based reanalysis protocol and subsequent amendments were approved by the institutional review boards (IRBs) of the three tertiary care centers that participated in the eligible randomized clinical trials (references 1 and 2). Due to the retrospective nature of the study and the use of an Excel datafile containing de-identified patient data during the conduct of the statistical analyses, the requirement for informed consent was waived. Before the initiation of the statistical analyses, access to electronic hospital records and electronic or hard-copy archives of the departments of Microbiology was authorized by the aforementioned IRBs, in order to (1) confirm prospectively collected data on infections/culture results (during the conduct of the included studies) and (2) retrospectively collect pertinent data on antibiotic resistance. Original protocol IRB approval numbers were as follows: Evaggelismos Hospital approval No. 14/9/1/2015; 401 Greek Army Hospital approval No. 3/2015/5/2/2015; Larissa University Hospital approval No. 58905/2014/14/1/2015. The protocol is registered with ClinicalTrials.gov (Identifier: NCT02408939).

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